# Novel SIRT1 Mutation Linked to Autoimmune Diabetes in Humans

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**Sirtuins are best known for their role in aging but also regulate many different biological processes. A study in this issue of *Cell Metabolism* (Biason-Lauber et al., 2013) now identifies a mutation in human SIRT1 causing a familial form of autoimmune diabetes.**

SIRT1 is an NAD-dependent protein deacetylase that has garnered a reputation for its diverse physiologic roles in metabolism, stress responses, tumorigenesis, aging, and immune regulation. *Sirt1* null mice develop autoantibodies and immune complex deposition disease resembling systemic lupus erythematosus (Sequeira et al., 2008). Furthermore, SIRT1 has been implicated in T cell regulation by affecting acetylation sites in the Foxp3 gene, a critical transcription factor involved in the function of regulatory T cells (Beier et al., 2012). SIRT1 has also been found to be required for T cell activation and for promoting clonal anergy, thus helping to maintain T cell tolerance (Zhang et al., 2009). In this issue of *Cell Metabolism*, a study of a family with multiple members affected by type 1 diabetes and inflammatory bowel disease reveals a novel point mutation, L107P, on the SIRT1 protein that appears responsible for the autoimmune phenotype (Biason-Lauber et al., 2013).

Type 1 diabetes is an autoimmune disease characterized by destruction of pancreatic β cells and a strong genetic component, mediated largely by MHC class II alleles but also other monogenic loci. The investigators of this study suspected a novel genetic link when they observed that, aside from the index patient, three other family members had juvenile-onset diabetes by the age of 15, while another had severe ulcerative colitis by age 16, highlighting the autoimmune propensity of this family and strong penetrance of the underlying genetic condition. Indeed, all affected individuals in this family were found to carry a L107P mutation on SIRT1. The mutation appears dominant, in that all carriers developed autoimmune disease, while noncarriers did not. This newly discovered polymorphism does not appear to be a common cause of autoimmune diabetes, however. The authors screened for the presence of the L107P mutation in over 2,000 sporadic and familial diabetic patients, concluding that in fact it is an exceedingly rare polymorphism, absent in all subjects tested. Moreover, this SIRT1 locus is not clearly within the recognized type 1 diabetes genes, and the common MHC genes linked with type 1 diabetes were not associated with the development of diabetes in this cohort, suggesting a different mechanism of disease.

In order to characterize the role of the L107 residue on SIRT1 function, the authors examined SIRT1 molecular stability, subcellular localization, interaction with other proteins, and enzymatic activity. While the L107P mutation lay outside of the sirtuin enzymatic core, the mutation nonetheless had a modest effect on its deacetylase activity. Interestingly, a recent report suggested that the deacetylase activity of SIRT1 is crucially dependent on its oligomeric state and that aggregate formation is modulated through phosphorylation of its Thr522 residue (Guo et al., 2012). It may therefore be possible that the SIRT1 L107P mutation, located within the N-terminal protein-binding domain, might also affect its oligomerization and thus enzymatic activity.

In view of the central role of SIRT1 in a number of biologic processes, the findings in this family question whether the mutation in SIRT1 affects immunologic tolerance, the target tissue, or both. Indeed, the development of T1D and other autoimmune manifestations is consistent with a broader effect on immune regulation that is not specific for one particular organ. In addition, SIRT1 may be important in determining susceptibility of the target tissue toward autoimmune attack—in this case, infiltration of the islets by immune cells, possibly involving the local production of oxidative species and thereby affecting the propensity of β cells to die. While overexpression of wild-type SIRT1 protects β cells from cytokine toxicity by suppressing the NF-κB signaling (Lee et al., 2009), retroviral transduction of SIRT-L107P in a β cell line, MIN6, in the present study resulted in increased levels of inflammatory mediators, including stimulated nitric oxide synthase activity and TNF, which have been implicated in the pathogenesis of type 1 diabetes. Moreover, the absence of SIRT1 appears to lead to islet vulnerability, as evidenced by hastened loss of insulin staining and presumably islet mass in response to multiple low-dose streptozotocin, a model of type 1 diabetes by inducing β cell damage with a pathologic immune response. Interestingly and perhaps unsurprisingly, increased inflammatory cytokines may also alter insulin sensitivity. Consistent with prior observation that increased expression of SIRT1 and its activator resveratrol is associated with improved insulin sensitivity (Sun et al., 2007), Biason-Lauber et al. found that SIRT-L107P increased insulin resistance in the index patient and in myoblasts in vitro. Therefore, it appears that the modulation of the cytokine milieu, both in the pancreas and in muscle, is important for insulin production and sensitivity in the context of diabetes.

This fascinating case highlights the interactions of inflammatory mediators and immune responses leading to the development of autoimmunity on a

genetic basis. Eisenbarth's original conceptualization of the pathogenesis of type 1 diabetes in 1986 described an initiating event that most likely incurred inflammation, triggering an unregulated autoimmune response as a major cause of β cell destruction. Based on this concept and the central role that SIRT1 plays in tissue and metabolic homeostasis and in immune regulation, it is conceivable that a mutation in this gene that might affect both cell damage and immune regulation could lead to autoimmunity (Figure 1). In considering other potential mechanisms of β cell death, there is emerging evidence that SIRT1 may regulate autophagy by complexing with the autophagy machinery and by modulating autophagy signaling via mTOR and FOXO, among other pathways (Lee et al., 2008; Hariharan et al., 2010). An intriguing possibility, therefore, is that pancreatic islet cells depend on SIRT1 for autophagy flux, which is essential for their survival (Jung et al., 2008). Lastly, as Biason-Lauber et al. suggest, dysregulation of cell death in islets may result in aberrant leakage of autoantigens, leading to activation of autoimmune effectors and amplifying the insulitis cascade. In this regard, we may have only glimpsed the complex role of SIRT1 in type 1 diabetes, and the questions raised by this study will fuel the discovery of new SIRT1 functions in metabolic control and autoimmune disease pathogenesis.

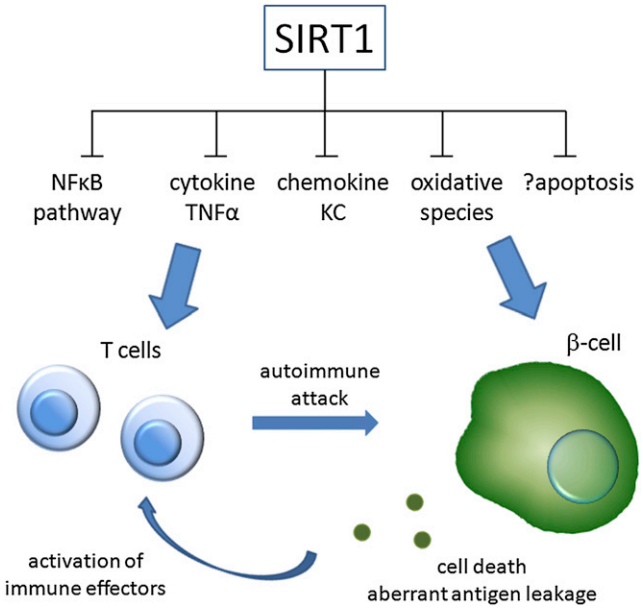


**Figure 1. SIRT1 Regulation of Lymphocytes and β Cells in Autoimmune Diabetes**

SIRT1 as a transcriptional regulator controls multiple cellular processes and signaling pathways that differentially affect the immune system and pancreatic β cells. A familial mutation in the SIRT1 protein renders affected individuals susceptible toward autoimmune diabetes and inflammatory bowel disease, highlighting a role for SIRT1 in regulating development of autoimmune disease.

## REFERENCES

Beier, U.H., Wang, L., Han, R., Akimova, T., Liu, Y., and Hancock, W.W. (2012). Sci. Signal. *5*, ra45.

Biason-Lauber, A., Boni-Schnetzler, M., Hubbard, B.P., Bouzakri, K., Brunner, A., Cavelti-Weder, C., Keller, C., Meyer-Boni, M., Meier, D.T., Brorsson, C., et al. (2013). Cell Metab. *17*, this issue, 448–455.

Guo, X., Kesimer, M., Tolun, G., Zheng, X., Xu, Q., Lu, J., Sheehan, J.K., Griffith, J.D., and Li, X. (2012). Scientific Reports *2*, 640.

Hariharan, N., Maejima, Y., Nakae, J., Paik, J., Depinho, R.A., and Sadoshima, J. (2010). Circ. Res. *107*, 1470–1482.

Jung, H.S., Chung, K.W., Won Kim, J., Kim, J., Komatsu, M., Tanaka, K., Nguyen, Y.H., Kang, T.M., Yoon, K.-H., Kim, J.-W., et al. (2008). Cell Metab. *8*, 318–324.

Lee, I.H., Cao, L., Mostoslavsky, R., Lombard, D.B., Liu, J., Bruns, N.E., Tsokos, M., Alt, F.W., and Finkel, T. (2008). Proc. Natl. Acad. Sci. USA *105*, 3374–3379.

Lee, J.-H., Song, M.-Y., Song, E.-K., Kim, E.-K., Moon, W.S., Han, M.-K., Park, J.-W., Kwon, K.-B., and Park, B.-H. (2009). Diabetes *58*, 344–351.

Sequeira, J., Boily, G., Bazinet, S., Saliba, S., He, X., Jardine, K., Kennedy, C., Staines, W., Rousseaux, C., Mueller, R., and McBurney, M.W. (2008). Exp. Cell Res. *314*, 3069–3074.

Sun, C., Zhang, F., Ge, X., Yan, T., Chen, X., Shi, X., and Zhai, Q. (2007). Cell Metab. *6*, 307–319.

Zhang, J., Lee, S.-M., Shannon, S., Gao, B., Chen, W., Chen, A., Divekar, R., McBurney, M.W., Braley-Mullen, H., Zaghouani, H., and Fang, D. (2009). J. Clin. Invest. *119*, 3048–3058.